Remarks

The Interview

Applicants, the licensee, and the undersigned greatly appreciated the opportunity to interview this application with the examiner, superviser David Isabella, and quality control specialist Greg Vidovich, on December 9, 2009, at the U.S. Patent Office.

The claims have been amended as discussed at the interview.

The term "comprising" has been replaced with "consisting of". As discussed, this more clearly distinguishes prior art devices which include materials such as stainless steel or collagen, in combination with biodegradable synthetic polymers.

The polymer has been amended to refer to synthetic biocompatible chemically degradable polymers. See original issued patent U.S. 6,348,069, col. 4, to col. 5, line 43. Explicit support for synthetic is found at col. 4, line 6. Explicit support for chemically biodegradable is found at col. 4, lines 2-4. Explicit support for synthetic rather than natural polymers is found at col. 4, lines 33-39. These amendments were made to distinguish any potential prior art using collagen or other polymers which are enzymatically degraded, not hydrolytically (chemically) degraded.

Claim 9 has been amended to refer to the preferred polymers.

Rejections Under 35 U.S.C. § 103

Claims 1, 2, 4, 9, and 11-14 were rejected under 35 U.S.C. § 103 (a) as obvious over U.S. Patent No. 5,207,705 to Trudell ("Trudell"). Claims 3, 18 and 19 were rejected under 103 as obvious over Trudell in combination with U.S. Patent No. 5,207,705 to Sparks, ("Sparks"). Claim 5 was rejected under 35 U.S.C. 103 as obvious over Trudell in combination with U.S. Patent No. 5,514,378 to Mikos ("Mikos"). Applicants respectfully traverse these rejections as applied to the amended claims.

When applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to:

(a) determining the scope and contents of the prior art;

(b) ascertaining the differences between the prior art and the claims at issue;

(c) resolving the level of ordinary skill in the pertinent art; and

(d) evaluating evidence of secondary considerations.

Graham v. John Deere, 383 US 1, 17-18, 148 U.S.P.Q. 459, 467 (1966). These four factors are traditionally referred to as the "Graham factors". The Graham factors were affirmed by the U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007).

Evidence of secondary considerations to be considered in an analysis under 35 U.S.C. § 103 include commercial success, long felt but unresolved needs, failure of others, etc. M.P.E.P § 2145, *citing Graham*, 383 U.S. at 17, 148 U.S. P.Q. at 467. Evidence may also include evidence that the claimed invention yields unexpectedly improved properties or that the claimed invention

possesses unexpected properties. M.P.E.P § 2145, *citing In re Dillon*, 919 F.2d 688, 692-93, 16 U.S.P.Q.2d 1897, 1901 (Fed. Cir. 1990).

Analysis

The Scope and Content of the Prior Art

U.S. Patent No. 5,207,705 to Trudell, et al. ("Trudell")

Trudell does not disclose a cell-matrix construct which is in the shape of a heart valve or valve leaflet, wherein the cells seeded thereon attach and proliferate in a three dimensional space.

As discussed at the interview, Trudell describes a device formed of a foam polyurethane and collagen. This composition is explicitly excluded by the language 'consisting of" and "synthetic chemically biodegradable polymer". Collagen is degraded enzymatically, not hydrolytically *in vivo*.

Trudell's construct cannot integrate into or grow with the host. The matrix does not provide the necessary biomechanical properties to serve as a heat leaflet or valve.

U.S. Patent No. 5,207,705 to Sparks

Sparks discloses a stainless steel device to hold a fabric mesh for use in forming tissue. It is not biodegradable, the polymeric portion does not provide the requisite biomechanical properties, it is not implantable and integratable into the host where it would have function like that of the native tissue. It does disclose implantation.

U.S. Patent No. 5,514,378 to Mikos ("Mikos")

Mikos discloses biocompatible porous polymer membranes prepared by dispersing salt particles in a biocompatible polymer solution. Mikos discloses that a three dimensional structure

can be manufactured from the membranes. The resulting three-dimensional foam or shape is a porous, biocompatible matrix to which cultured cells can attach and proliferate, and can be used for organ transplant or reconstructive surgery (Mikos, column 3, lines 25-45). Mikos does disclose seeding with cells.

Ascertaining the differences between the prior art and the claims at issue

Tissue engineering is a science which utilizes basic principles from life sciences and engineering to create cellular constructs for transplantation. Numerous polymers and techniques have been described in the prior art for use in tissue engineering; however, one of ordinary skill in the art is aware that the availability of polymers and methods has not directly translated to successful construction of replacement tissues. For decades, people had tried to make artificial hearts, relying on machines, processed animal or cadaver heart valves, and combinations thereof, just as the art cited by the examiner demonstrates. With respect to tissue engineered heart valves in particular, despite the availability of polymers and methods described in the art of tissue engineering, it was not until 1995 that there was a major breakthrough in tissue engineered valves, which enabled production of functioning tissue engineered heart valves (*See* Mol, et al., *Circulation*, 114(Suppl 1):152-158 (2006) ("Mol") and Schmidt, et al., *Swiss Med Wkly*,135:618-23 (2005) ("Schmidt") (copies of which were previously submitted for the convenience of the examiner).

As noted in Schmidt, many of the available heart valve prosthesis did not actively adapt to the physiological environment such as pressure changes and mechanical demands, because they remained inherently different from the tissue they replaced (see Schmidt, first page, left. col.

2nd para.). Schmidt further discloses that these limitations motivated the exploration of novel approaches towards valve replacement. Schmidt goes further to cite the studies by Shinoka (in 1995) as the first milestone in heart valve tissue engineering (see Schmidt, first page, right col. 2nd para.). Thus, in spite of the availability of polymers and bioengineering techniques, Applicants were the first to figure out how to make this technology actually work. They showed that the structures could function just as the native tissue and could integrate into ***and grow with the host***, to provide a cure, not just a replacement component, for the heart valve or leaflet that was being replaced.

As discussed during the interview, the first tissue engineering was done with cells that formed amorphous organs such as liver and pancreas, which have functional, but not structural, requirements. Next there was a great deal of work, including that of Mikos, that looked at making structural tissues such as cartilage. However, these tissues did not have moving structural requirements - they are relatively stationary. Blood vessels and heart valves must not only have function and structure, they must be able to withstand enormous, frequently applied stresses and strains over prolonged periods of time. This required growing the cells on the matrix in a bioreactor, either an animal or human or an artificial bioreactor that could apply stress and strain to the growing and forming tissue. This was applicants' discovery.

Mikos discloses biocompatible polymers that can be used to make a three dimensional matrix of a desired shape for use in making tissue. Mikos does not disclose how to make a cell matrix construct for use as a heart valve. The intended use is relevant, because, while biocompatible polymers are known in the art, the challenge with respect to tissue engineering has

been to make functional organs using these polymers. All Mikos is concerned with is shaping a polymer into a three dimensional structure, which can be used to make structural tissue such as cartilage or bone where a static (i.e., non-moving, not subject to stress or strain) tissue shape is integral to function (Mikos, col. 2, lines 45-54). One of ordinary skill in the art would understand that disclosing a biocompatible polymer is not tantamount to disclosing tissue constructs made of that polymer. Furthermore, disclosing characteristics relevant to making structural tissue such as cartilage or bone for example, does not make obvious using the same polymer to make functional tissue such as kidneys or heart valves with any expectation of success, absent explicit direction on how to arrive at such a construct. There is no disclosure in Mikos that one can form a structure that can move and function as the structure to be replaced, such as a heart, which must move repeatedly, be elastic and flexible, and withstand enormous strain.

Applicants have unexpected results

The most fundamental reason why the claimed subject matter is patentable is that no one could have predicted, nor have reasonably expected, a synthetic polymeric matrix seeded with cells to form a functioning heart valve or leaflet that could provide the required function - essential to life itself - and become integrated into the host after transplantation, so that it continued to provide the essential function for the host to live and to grow with the host. This technology provides a means to achieve replacement heart components that NO other technology can: a tissue engineered heart component(s) that

(1) INCORPORATES FULLY into the patient,

(2) provides COMPARABLE BIOMECHANICAL PROPERTIES as the component(s) being replaced, and

(3) GROWS with the patient.

The features are completely unexpected, not just in view of the prior art, but in view of the general knowledge in the field. The priority date of the application that originally issued as U.S. Patent No. 6,348,069, and its parent U.S. Patent No. 5,855,610, is May 19, 1995. Further studies were conducted and published by the inventors. Copies of publications reporting the results of these studies were previously submitted:

Breuer, et al., "Tissue Engineering Lamb Heart Valve Leaflets" *Biotech. Bioeng.* 50:562-567 (1996)

Zund, et al., "The in vitro construction of a tissue engineered bioprosthetic heart valve" *Eur. J. Cardio-thoracic Surg.* 11:493-497 (1997)

Hoerstrup, et al., "Functional Living Trileaflet Heart Valves Grown in vitro" *Circulation*, 102:III-44-III-49 (2000).

Sodian, et al., "Early In vivo Experience with Tissue-Engineered Trileaflet Heart Valves" *Circulation*, 102:III-22-III-29 (2000).

Stock, et al., "Tissue Engineering of Heart Valves- Current Aspects" *Thorac. Cariov. Surg.* 50:184-193 (2002).

The references show, step by step, how they have shown that one can make the matrices as claimed, using different synthetic biodegradable materials, seeded with different cell types, cultured *in vitro* or *in vivo*, then implanted into large animal models (lambs) to demonstrate that

they can form heart valves and leaflets that are histologically comparable to native tissue, functionally comparable to native tissue, integrate into a natural heart, and grow with the heart.

Results of this magnitude must be considered in making a rejection under 35 U.S.C. 103. The Supreme Court has made it clear that if the outcome could not have been predicted, based on the prior art by one of ordinary skill in the art at the time the application was filed, it is not obvious. Thus, Applicants should be re-granted a patent with claims having sufficient scope to allow the further development of this technology so it will be made available to those in need.

For the foregoing reasons, Applicants submit that claims 1-5, 8, 11-14, 18, and 19 are patentable.

Respectfully submitted,

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